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Evaluation of Respiratory Functions with Spirometry in Patients with SARS-CoV-2 Pneumonia

Tahsin Karaaslan[1]*, Esra Karaaslan[2], Omer Uysal[3], Mehmet Gunduz[4]

1 Medeniyet University, Goztepe Prof. Dr. Suleymen Yalcin City Hospital, Dept of Nephrology, Istanbul, TR
2 Medipol University Sefakoy Hospital, Department of Chest Diseases, Istanbul, TR
3 Bezmialem Vakif University, Medical Faculty, Department of Medical Statistics and Informatics, Istanbul, TR
4 Medipol University Sefakoy Hospital, Department of Pediatrics, Istanbul, TR

*** Corresponding Author:** Tahsin Karaaslan **E-mail:** drtakaraslan@hotmail.com

ABSTRACT

Objective: This study aims to evaluate respiratory functions in patients Coronavirus disease-2019 (COVID-19) with and without pneumonia.

Material and Methods: This single-center, prospective study included a total of 72 patients who were diagnosed with COVID-19 infection as confirmed by real-time reverse transcriptase polymerase chain reaction (rtPCR). The patients were divided into two groups according to the physical and thoracic computed tomography (CT) findings as mild symptomatic patients without COVID-19 pneumonia (n=26) and symptomatic cases with COVID-19 pneumonia (n=46). Respiratory functions were evaluated by spirometry in the second and fourth months of the disease onset.

Results: The average age of 72 patients, 41 of whom were men, was 40.5±12.27 years. Thoracic CT revealed infiltrations compatible with COVID-19 pneumonia in 46 (63.9%) patients. Hypertension (12.5%) and diabetes (5.6%) were the most common comorbidities. When the results of the patients with and without pneumonia at the second and fourth months were compared, there was no significant difference between the forced expiratory volume in the first second (FEV1) (p1=0,975, p2=0,291), forced vital capacity (FVC) (p1=0,668, p2=0,481) and FEV1/FVC ratio (FER) (p1=0,378, p2=0,980) values. When the repeated Anova test was used in the comparison of the two visit differences between the groups, it was seen that there was no difference in any heading (FVC: p=0.077; FEV1: p=0.150; FER: p=0.355).

Conclusions: Our study results show no significant difference in the pulmonary function tests of patients with mild and moderate COVID-19 pneumonia at two and four months, compared to those without pneumonia However, additional studies are needed for severe and critical cases.

Key Words: COVID-19, pulmonary function tests, SARS-CoV-2, pneumonia, spirometry

INTRODUCTION

In December 2019, several cases of pneumonia of unknown causes were found in Wuhan, Hubei province of China, which were later identified as novel coronavirus-2019 (2019-nCoV), a novel beta-coronavirus belonging to subgenus (**1**). As its genome is phylogenetically similar to that of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, it is termed as SARS-coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) later named the virus as the novel coronavirus-2019 (COVID-19) (**2**). Although COVID-19 involves many tissues in the human body, the lungs are the main organs affected by the virus. Previous studies have shown that survivors of SARS and MERS have persistent lung impairment for months or even years (**3-5**). The SARS-CoV-2 enters the pulmonary epithelial cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors and induces viral replication, leading to apoptosis of alveolar type 2 epithelial cells. In addition to its direct cytopathic effect, the presence of inflammation and elevated cytokine levels cause diffuse alveolar damage and the formation of fibrin-rich exudates (i.e., hyalin membranes). At the end of this pathological process, recovery occurs with scarring in the lung epithelium and fibrosis in the lung parenchyma (**6**).

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Hariri et al. (7) reported that histopathological changes in asymptomatic cases were less severe than in symptomatic cases. Theoretically, it is not unexpected that survivors may have impaired pulmonary functions.

Histopathological findings of lungs are often based on post-mortem studies in COVID-19. These are already severe and critical cases. There is a limited number of evidence regarding the histopathological lung findings of mild and non-critical COVID-19. The disease course may mild-to-moderate in the majority of cases worldwide and future studies would shed light into the lung functions of recovered patients, which would be helpful to decide treatment and follow-up. Therefore, in the present study, we included mild-to-moderate COVID-19 cases.

MATERIALS and METHODS

Study design and study population

This single-center, prospective study was conducted at Department of Chest Diseases of a tertiary care center between June 24th, 2020 and December 15th, 2020. Prior to the study and all diagnostic and therapeutic procedures, all participants were informed in detail, and a written informed consent form was obtained. The study protocol was approved by the local Ethics Committee (No: 2020/0407-Date: 24.06.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients aged between 18 and 65 years with a confirmed diagnosis of COVID-19 by real-time reverse transcriptase polymerase chain reaction (RT-PCR) were screened. A total of 72 patients who had positive RT-PCR from nasopharyngeal swab samples. As the pulmonary function tests (PFTs) are aerosol-producing procedures and entail a risk of infection for both patients and healthcare workers (HCWs), these tests were avoided in our daily practice during the COVID-19 pandemic. Only the patients who met the inclusion criteria of the study underwent PFTs. Those having myocardial infarction within the last week, stroke within the past month, decompensated heart failure, malignant hypertension, undergoing thoracic, abdominal, ear, or eye operations within the past month, pregnancy, an active respiratory infection, having difficulties in cooperation with the HCWs, and those having anatomical chest deformities were excluded from the study. All patients underwent thoracic computed tomography (CT). According to the physical and imaging examination findings, the patients were divided into two groups as mild symptomatic patients without COVID-19 pneumonia on CT (n=26) and symptomatic cases with COVID-19 pneumonia on CT not requiring oxygen support (n=46). Patients with severe pneumonia defined as the radiographic evidence of pneumonia, a respiratory rate of $\geqslant$30 breaths/min, oxygen saturation of $\leqslant$93% without severe dyspnea at rest and with >50% increase in the lung lesions within the last 24 to 48 hours; critically ill patients (i.e., septic shock, requiring non-invasive or invasive mechanical ventilation, multiple organ failure, and requiring intensive care) were also excluded from the study.

The CT images were quantitatively evaluated according to the involvement due to the inflammatory lesions of the total lung parenchyma and scored as follows: 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%), and 4 (76-100%).

Study procedures

Demographic and clinical characteristics and comorbidities of all patients were recorded. Prior to PFTs, body temperature was measured, and symptoms were questioned for all patients. Those who tested negative for two consecutive RT-PCR within the past 48 to 72 hours underwent PFTs. During the measurement, a disposable bacterial and viral filters were used for each patient. The technician who performed the PFTs complied with the donning/doffing procedures of the personal protective equipment (PPE). The onset of the disease was considered the date of the first symptom onset. The PFTs were repeated at minimum of 60 days and 120 days after the disease onset, respectively.

All CT images were acquired at the end of inhalation using a 16-slice CT scanner (SOMATOM Scope Power; Siemens Healthineers, Forchheim, Germany). The PFTs were performed by technicians in the PFT laboratory using a spirometer (SpiroLab III®; MIR Medical International Research, Rome, Italy). All PFTs were carried out in accordance with the 2019 American Thoracic Society (ATS) / European Respiratory Society (ERS) technical statement (8). The spirometry was performed in accordance with the prespecified national spirometry and laboratory standards and repeatability and precision criteria (9). The spirometer was calibrated on a regular basis. All PFT results were expressed in percentage of the predicted normal values.

Statistical Analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation (SD), median (min-max), or number and frequency, where applicable. The Student's t-test was used to compare quantitative variables between the groups. The repeated measures analysis of variance (ANOVA) was performed to analyse the difference between the measurements at two-time points. The chi-square ($\chi 2$) test was used to compare categorical variables. The Pearson correlation coefficient was used to examine the relationship between the quantitative variables. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 41 (56.9%) were males, and 31 (43.1%) were females with an overall mean age of 40.5±12.27 (range, 18 to 64) years. There was no significant difference in the sex of the patients with and without COVID-19 pneumonia ($\chi 2$=1.93, p=0.164). However, the mean age was significantly higher in the patients with COVID-19 pneumonia compared to those without (44.91±10.90 years vs. 32.69±10.71 years, respectively; t=4.60, p<0.001). Thoracic CT revealed normal findings in 36.1% (n=26) of the patients, while it showed lung infiltrations compatible with SARS-CoV-2 pneumonia in 63.9% (n=46). The overall mean bodyweight of the patients was 79.51±15.11 kg, and the mean body mass index (BMI) was 27.96±5.09 kg/m^2. There was a significant correlation between body weight and BMI and CT positivity (t=3.52, p<0.001). The baseline demographic and clinical characteristics of the patients are shown in **Table1**.

Comorbidities of the patients are summarized in **Table 2**. The most common comorbidities included hypertension (n=9,

12.5%), diabetes (n=4, 5.6%), and coronary artery disease (n=4, 5.6%). Only three patients (4.2%) had a previous history of asthma.

Eleven (15.1%) of the patients were smokers. There was no significant correlation between smoking and CT positivity (p=0.735). None of the patients required non-invasive or invasive mechanical ventilation. The most common symptoms were fever (n=61, 84.7%) and dry cough (n=38, 52.8%), followed by fatigue (40.3%), myalgia (33.3%), dyspnea (22.2%), and loss of taste and smell (6.9%). We found a significant correlation between dyspnea and CT positivity ($\chi 2$=7.95, p=0.005), while there was no significant relationship between the other symptoms and CT positivity (p>0.05).

There was no significant difference in the forced vital capacity (FVC) of the patients with mild and moderate pneumonia at two and four months, compared to those without pneumonia (Visit 1: t=-0.431, p=0.668; Visit 2: t=0.709, p=0.481). In addition, there was no significant difference in the forced expiratory volume in one second (FEV1) of the patients with mild and moderate pneumonia at two and four months, compared to those without pneumonia (Visit 1: t=-0.032, p=0.975; Visit 2: t=1.063, p=0.291). No significant difference in the FEV1/FVC ratio (FER) of the patients with mild and moderate pneumonia at two and four months, compared to those without pneumonia (Visit 1: t=0.888, p=0.378; Visit 2: t=0.025, p=0.980) (**Table 3**). The FEV1 (>80%), FVC (>80%), and FER (>70%) values were found to be normal in three patients with a previous history of asthma at two and four months. There was no significant difference in the delta-FVC, delta-FEV1, and delta-FER values between the patients with and without pneumonia (t=1.794, p=0.077; t=1.455, p=0.150; t=-0.931, p=0.355, respectively) (**Table 3**).

According to the repeated measures ANOVA test, there was no significant difference in the other variables between the measurements at two-time points (FVC: F=3.218, p=0.077; FEV1: F=2.118, p=0.150; FER: F=0.867, p=0.355, respectively) (**Table 4**).

In the multivariate linear regression analysis, independent variables such as age, sex, duration, and the first visit measurements and dependent variables with delta differences were analysed, and no significant difference was observed.

According to the radiological scoring of all patients, 0 was assigned to 36% (n=26), 1 to 37.5% (n=27), 2 to 22.2% (n=16), 3 to 4.2% (n=3), and 4 to 0.0% (n=0) of the patients. Based on the radiological scoring in an ordinal scale, no statistically significant correlation between any of the variables including delta differences was observed (non-parametric Spearman correlation coefficient, p>0.05).

In addition, there was no statistically significant correlation between the radiological scores (0-1-2-3) and FEV1, FVC, FEV1/FVC, peak expiratory flow (PEF), and forced expiratory flow (FEF)25-75 at two- and four-month measurements (r=0.08, p=0.947; r=-0.015, p=0.901; r=0.038, p=0.749; r=-0.044, p=0.716; r=-0.089, p=0.457; r=0.062, p=0.606; r=-0.054, p=0.650; r=0.065, p=0.587; r=-0.129, p=0.278; r=0.041, p=0.732, respectively). Similarly, we found no significant correlation between the radiological scores (0-1-2-3) and delta-different FEV12-1 (r=-0.067, p=0.576), delta-different FVC2-1 (r=-0.132, p=0.269), delta-different PEF2-1 (r=0.163, p=0.173), and delta-different FEF25-75(2-1) (r=0.043, p=0.718).

Of 46 patients with COVID-19 pneumonia on CT, there were minimal, but persistent radiographic abnormalities in only three patients (6.5%). The high-resolution CT revealed normal findings in the remaining patients. The PFTs yielded no obstructive or restrictive pattern in the patients with minimal radiographic sequelae (p>0.05).

Table 1. Baseline demographic and clinical characteristics of patients

	Total	CT group	n	Min	Max	Mean	SD	*p value*
Age (year)	n=72 Mean=40,5 ±12,27 range;18-19	CT (-) CT (+)	26 46	18 22	50 64	32,69 44,91	10,71 10,90	p<0,001 t=-4,60
Sex	Male (n=41); 59.9% Female (n=31) 43.1%	CT (-) CT (+)	Female: n=14 (53,8%) Female: n=17 (36,9%)		Male: n=12 (46,2%) Male: n=29 (63,1%)			p=0,164 χ^2=1,93
	Total	**CT group**	**n**	**Min**	**Max**	**Mean**	**SD**	***p value***
Weight (kg)	Mean=79,51 ±15,11	CT (-) CT (+)	26 46	48 54	100 117	71,42 84,09	15,087 13,212	p<0,001 t=-3,71
Height (cm)	Mean=168,68 ±9,16	CT (-) CT (+)	26 46	145 153	187 195	167,96 169,09	8,973 9,342	p=0,620 t=-0,49
BMI (kg/m^2)	Mean=27,96 ±5,09	CT (-) CT (+)	26 46	17,01 21,09	41,38 39,54	25,35 29,43	5,41 4,30	p=0,001 t=-3,52
SBP (mmHg)	Mean=125,76±13,41	CT (-) CT (+)	26 46	100 100	150 180	122,69 127,50	8,48 15,34	p=0,91 t=-1,71
DBP (mmHg)	Mean=76,65 ±8,85	CT (-) CT (+)	26 46	68 64	100 100	75,08 77,54	7,205 9,610	p=0,259 t=-1,14

$\chi 2$=Pearson chi-square, t=t-test for equality of means. CT=computed tomography; Min=minimum, max=maximum, SD=standard deviation, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure.

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Table 2. Comorbidities of patients

	Total n	Total %	CT_group	n	%	*p value*
Fever	61	84.7	CT (-) CT (+)	22 39	84.6 84.8	p=1,000 (Fisher's)
Dry cough	38	52.8	CT (-) CT (+)	10 28	38.5 60.9	p=0,067 χ^2=3,35
Dyspnea	16	22.2	CT (-) CT (+)	1 15	3.8 32.6	p=0,005 χ^2=7,95
Myalgia	24	33.3	CT (-) CT (+)	10 14	38.5 30.4	p=0,488 χ^2=0,48
Fatigue	29	40.3	CT (-) CT (+)	9 20	34.6 43.5	p=0,461 χ^2=0,54
Loss of taste and smell	5	6.9	CT (-) CT (+)	1 4	3.8 8.7	p=0,647 (Fisher's)
Hypertension	9	12.5	CT (-) CT (+)	1 8	3.8 17.4	p=0,143 (Fisher's)
Diabetes	4	5.6	CT (-) CT (+)	0 4	0 8.7	p=0,289 (Fisher's)
Coronary artery disease	4	5.6	CT (-) CT (+)	1 3	3.8 6.5	p=1,000 (Fisher's)
Asthma	3	4.2	CT (-) CT (+)	1 2	3.8 4.3	p=1,000 (Fisher's)
Smoker	11	15.3	CT (-) CT (+)	3 9	11.5 17.4	p=0,735 (Fisher's)

CT= Computed Tomography.

Table 3. PFT results of patients with and without CT positivity

	CT group	n	Mean %	SD	t-test for equality of means t	*p* value
FEV1 Visit 1	CT (-) CT (+)	26 46	96,92 97,02	13,79 11,81	-0,032	0,975
FEV1 Visit 2	CT (-) CT (+)	26 46	98,50 95,35	14,59 10,43	1,063	0,291
FVC Visit 1	CT (-) CT (+)	26 46	94,81 96,11	13,25 11,73	-0,431	0,668
FVC Visit 2	CT (-) CT (+)	26 46	95,69 93,57	13,83 11,24	0,709	0,481
FER Visit 1	CT (-) CT (+)	26 46	102,08 100,91	4,93 5,56	0,888	0,378
FER Visit 2	CT (-) CT (+)	26 46	101,88 101,85	5,40 6,24	0,025	0,980
PEF Visit 1	CT (-) CT (+)	26 46	90,92 91,26	20,97 19,19	-0,069	0,945
PEF Visit 2	CT (-) CT (+)	26 46	90,04 95,26	19,09 20,84	-1,052	0,296
FEF_{25-75} Visit 1	CT (-) CT (+)	26 46	102,35 96,26	20,86 22,15	1,143	0,257
FEF_{25-75} Visit 2	CT (-) CT (+)	26 46	103,58 100,61	24,34 23,40	0,510	0,612
Delta_diff_FVC_2_1	CT (-) CT (+)	26 46	0,88 -2,54	7,15 8,12	1,794	0,077
Delta_diff_FEV_2_1	CT (-) CT (+)	26 46	1,58 -1,67	8,05 9,64	1,455	0,150
Delta_diff FEV1/FVC_2_1	CT (-) CT (+)	26 46	-0,19 0,93	5,35 4,68	-0,931	0,355
Delta_diff_PEF_2_1	CT (-) CT (+)	26 46	-0,88 4,00	16,59 15,51	-1,252	0,215
Delta_diff_FEF_{25_75}_2_1	CT (-) CT (+)	26 46	1,23 4,35	18,95 23,39	-0,564	0,564

t= t-test for equality of means. CT= computed tomography; SD= standard deviation, FEV1=forced expiratory volume in one second, FVC=forced vital capacity, FER= forced expiratory volume in one second/forced vital capacity ratio, PEF=peak expiratory flow, FEF=forced expiratory flow, FEF25-75=forced expiratory flow at 25-75% of the pulmonary volume.

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Table 4. Frequency of abnormal PFT results and relationship between groups

		CT group		Total	*p* value (Fisher's exact test)
		CT (-)	CT (+)		
FVC Visit 1 <80%pred	N	3	3	6	0,661
	% within CT group	11.5%	6.5%	8.3%	
FVC Visit 2 <80%pred	N	2	3	5	1,000
	% within CT group	7.7%	6.5%	6.9%	
FEV1 Visit 1 <80%pred	N	2	3	5	1,000
	% within CT group	7.7%	6.5%	6.9%	
FEV1 Visit 2 <80%pred	N	1	3	4	1,000
	% within CT group	3.8%	6.5%	5.6%	
FER Visit 1 <70%pred	N	0	0	0	
	% within CT group	0	0	0	
FER Visit 2 <70%pred	N	0	0	0	
	% within CT group	0	0	0	
PEF Visit 1 <65%pred	N	3	5	8	1,000
	% within CT group	11.5%	10.9%	11.1%	
PEF Visit 2 <65%pred	N	1	3	4	1,000
	% within CT group	3.8%	6.5%	5.6%	
FEF_{25-75} Visit 1 <65%pred	N	1	3	4	1,000
	% within CT group	3.8%	6.5%	5.6%	
FEF_{25-75} Visit 2 <65%pred	N	0	2	2	0,532
	% within CT group	0.0%	4.3%	2.8%	
Repeated measures ANOVA (multivariate analysis)				F	*p* value
FVC	Visit 1*2			0,754	0,388
	Visits* CT group			3,218	0,077
FEV1	Visit 1*2			0,002	0,965
	Visits CT group			2,118	0,150
FER	Visit 1*2 (Pillai's Trace)			0,376	0,542
	Visits *CT group (Pillai's Trace)			0,867	0,355
PEF	Visit 1*2			0,637	0,427
	Visits *CT group			1,567	0,215
FEF_{25-75}	Visit 1*2			1,077	0,303
	Visits *CT group			0,336	0,564

CT= computed tomography; SD= standard deviation, FEV1= forced expiratory volume in one second, FVC= forced vital capacity, FER= forced expiratory volume in one second/forced vital capacity ratio, PEF= peak expiratory flow, FEF= forced expiratory flow, FEF25-75= forced expiratory flow at 25-75% of the pulmonary volume.

DISCUSSION

From the beginning of the declaration of COVID-19 pandemic by the WHO on March 11th, 2020, a total of 28,637,952 positive cases were identified with 917,417 deaths until September 14th, 2020 (10). Patients may present with a wide range of symptoms from asymptomatic or mild disease to septic shock and multiple organ dysfunction. The disease is mainly classified into four types: mild, moderate, severe, and critical (11). The diagnosis of COVID-19 is made based on clinical findings, as well as laboratory and imaging test results; however, it is not always possible to establish the definitive diagnosis due to non-specific nature of the clinical and imaging signs of COVID-19.

On the molecular basis, the diagnosis is confirmed using RT-PCR which can qualitatively detect the nucleic acid from the nasopharyngeal/oropharyngeal swabs (12). The sensitivity of RT-PCR is 36% for oropharyngeal swabs and up to 63% for nasopharyngeal swabs (13). However, a single negative swab test alone does not rule out SARS-CoV-2 infection and there is still no ideal specimen for the definitive diagnosis of COVID-19 (14). In repeated negative test results, serologic testing (i.e., IgM and IgG antibodies) can guide the diagnosis (15).

The PFTs are useful, non-invasive tests for screening, diagnosis, and follow-up of respiratory track diseases. Spirometry is the most common type of PFTs and is a physiological test that measures the inhalation and exhalation flow/volumes of air as a function of time (16).

The most common parameters measured in spirometry during forced breathing maneuvers include vital capacity (VC), FVC, FEV, forced expiratory flow (FEF), and peak expiratory flow (PEF).

Previous studies have demonstrated that SARS-CoV-2 infection can cause a variety of symptoms ranging from mild infiltration to acute respiratory distress syndrome (ARDS). In a postmortem biopsy study, Xu et al. (17) reported a case of COVID-19 who died from ARDS. The histological examination showed diffuse alveolar damage with cellular fibromyxoid exudates and evident desquamation of pneumocytes and hyaline membrane formation with diffuse alveolar damage, indicating ARDS. In another postmortem study, Hanley et al. (18) showed diffuse alveolar damage and hyaline membrane formation in a COVID-19 case. In addition, Pan et al. (19) examined the imaging characteristics of the COVID-19 pneumonia in 63 confirmed cases and reported fibrous stripes in 11 (17.5%) patients as assessed by CT imaging. Recent autopsy studies also revealed that the lungs of the COVID-19 non-survivors were filled with clear liquid jelly containing probably hyaluronan, which has a high water-absorption capability (17). Elevated inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α) are potent inducers of hyaluronan synthesis, which are seen in the lungs of COVID-19 cases (20). In these patients, both the direct cytopathic effect of the virus and exaggerated inflammatory response caused by elevated proinflammatory cytokines such as IL-1, IL-6, and

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TNF-α result in damage in the alveolar epithelial cells and endothelial cells. Consequently, the connection between the cells is disrupted, leaking into the interstitial and alveolar spaces, and ARDS develops (10). Elevated cytokine expression has been shown to induce fibroblast migration and proliferation, thereby, resulting in lung fibrosis (21). The ACE2, itself, acts as a protective protein against the fibroblast cascade and reduced ACE2 in COVID-19 with increased angiotensin I and II contributes to the development of lung fibrosis. This theory can explain the higher mortality rates in patients with obesity, hypertension, and cardiovascular diseases in which baseline ACE2 levels are lower (10).

Incidental histopathological changes were found in the pathological examinations of 14 patients who were asymptomatic in terms of COVID-19 and were found to have new coronavirus infection after lung nodule resection (7). Of these, Kuang et al. explained that they detected changes such as interstitial pneumonia and hyaline membrane related to the new coronavirus in their lung cancer tissue sampling (22). The majority of cases have been reported proteinaceous exudate, pneumocyte hyperplasia, irregular chronic inflammation and focal edema with multinucleated pneumocytes (23, 24). Hariri et al. reported that histopathological changes in asymptomatic cases were less severe than in symptomatic cases (7). In their series of seven cases by Chai et al., they stated that only one patient had changes compatible with interstitial inflammation, while there were no changes associated with SARS-CoV-2 in the other six patients (25). However, in this study, there is no clear information regarding the pre-operative presence of COVID-19 infection in six of the seven cases. These studies have shown that asymptomatic patients may have mild histopathological changes. Histopathological changes in severe and critical cases were revealed by postmortem studies. However, we do not have enough information about what kind of histopathological changes occur in symptomatic mild and moderate cases. On the other hand, it is still unclear whether these pathological alterations in the lung parenchyma lead to sequelae in the long-term or how they affect the pulmonary functions in the mid- and long-term.

In a study, Zha et al. (26) reported two COVID-19 cases who developed severe ARDS. During three-month follow-up, although most of the ground-glass opacities resolved, there were fibrotic changes in bilateral lungs on thoracic CT with worse lung ventilation compatible with the restrictive pulmonary disease (FVC: 62.3%, FER: 80.1%). In another study investigating long-term pulmonary function and physiological features of 55 COVID-19 survivors, Zhao et al. (27) excluded critical cases. There were still radiological and physiological abnormalities in three-fourth of the patients three months after discharge. Similarly, Mo et al. (28) found impaired diffusion capacity to be the most frequent abnormality of lung function in discharged COVID-19 survivors. However, there was no significant difference in the other ventilatory defects including FEV1, FVC, and FER among the survivors with different severity of disease. In a randomized-controlled study, Liu et al. (29) examined the effect of respiratory rehabilitation training in elderly patients with COVID-19. The authors reported that this patient population had different degrees of disorders in respiratory function after discharge, possibly due to residual fibrotic lesions and reduced respiratory muscle strength and that respiratory rehabilitation could significantly improve the lung function. Furthermore, Frija-Masson et al. (30) evaluated functional characteristics of 50 patients with COVID-19 pneumonia one month after infection and reported impaired lung function with a mix of restrictive and low diffusion patterns in more than half of the patients, indicating no association with the severity of the disease. In our study, we found no significant difference in the FVC of the patients with mild and moderate pneumonia at two and four months, compared to those without pneumonia (Visit 1: t=-0.431, p=0.668; Visit 2: t=0.709, p=0.481). In addition, there was no significant difference in the FEV1 pneumonia (Visit 1: t=-0.032, p=0.975; Visit 2: t=1.063, p=0.291) and FER (Visit 1: t=0.888, p=0.378; Visit 2: t=0.025, p=0.980) of the patients with mild and moderate pneumonia at two and four months, compared to those without pneumonia. In addition, the repeated measures ANOVA test revealed no significant difference in the other variables between the measurements at two time points (FVC: F=3.218, p=0.077; FEV1: F=2.118, p=0.150; FER: F=0.867, p=0.355, respectively). These results are consistent with the findings of Mo et al. (28) At the time of the first visit, abnormalities were observed in FVC (68 to 78%pred) in six patients (8.3%) and in FEV1 (71 to 78%pred) in five patients (6.9%), while, the FER value was normal (>70%pred) in all patients. This finding indicates mild restrictive spirometric patterns. In four patients (5.5%), the FEF25-75 was abnormal (46 to 64% pred), compatible with small airway obstruction. At the time of the second visit, abnormalities were seen in FVC (66 to 76%pred) in five patients (6.9%) and in FEV1 (69 to 76%pred) in four patients (5.5%); however, the FER value was normal in all patients. In only two patients (2.8%), the FEF25-75 was abnormal (55 to 62%pred), compatible with small airway obstruction. On the other hand, there was no statistically significant difference between the patient groups at two different time points (p>0.05). We also found no significant difference in the delta-FVC, delta-FEV1, and delta-FER values between the patients with and without pneumonia (p=0.077, p=0.150, and p=0.355, respectively).

Based on the radiological scoring in an ordinal scale, no statistically significant correlation between any of the variables including delta differences was observed (non-parametric Spearman correlation coefficient, p>0.05).

Although there was no significant difference in the sex between the patients with and without COVID-19 pneumonia (p=0.164), the mean age was significantly higher in those with pneumonia (p<0.001). This can be attributed to the fact that viruses have the ability to penetrate into the alveolar epithelial cells easily due to decreased mucociliary activity in advanced age, thereby, leading to the reduced regenerative capacity of the alveolar epithelial cells (6).

In a large-scale meta-analysis, the most common symptoms of COVID-19 were fever (81.2%), dry cough (62.9%), dyspnea (26.9%), and loss of taste (25.4%) (31). In our study, the most frequent symptoms were fever (84.7%), dry cough (52.8%), fatigue (40.3%), myalgia (33.3%), dyspnea (22.2%), and loss of taste and smell (6.9%). Although we observed no significant difference in the fever, dry cough, myalgia, and fatigue between the patients with and without COVID-19 pneumonia, we found a significant correlation between dyspnea and CT positivity (p=0.005). This finding is also

consistent with one of our previous reports including 206 RT-PCR-confirmed COVID-19 cases and showing a link between critical illness and CT positivity (**32**).

Limitations

The main limitation of the present study is the lack of homogeneous distribution of the patients between the groups and the relatively small sample size in the mild symptomatic patient group without COVID-19 pneumonia. In addition, the pulmonary functions of the patients before COVID-19 infection are not fully known, which may have led to incomplete interpretation of the measured values during the study. The unequal number of patients in each radiological scoring group is also another limitation which may have led to bias in the statistical calculation. Further prospective studies are warranted to gain a better understanding of the respiratory functions in severe and critical cases with SARS-CoV-2 pneumonia including those having 3-4 radiological scores.

CONCLUSION

In conclusion, our study results showed no significant difference in the PFT results of the patients with confirmed mild and moderate COVID-19 pneumonia at two and four months, compared to those without pneumonia. No obstructive or restrictive spirometric patterns were observed. However, further large-scale studies are needed in severe and critically ill pneumonia cases.

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